REMARKS

Claims 1, 5-9, 11-15, 20-25, 27, 29, 31-33, 35-39, 41, 42, 44-49, 51-59 and 61 are being examined and all stand rejected.

Specification

Applicants have amended the specification to reflect that the parent application is now an issued U.S. patent. The addition of the priority claim in the Preliminary Amendment that accompanied filing of this application mentioned only the parent application, which, at that time, had not yet issued. No other changes to the specification have been made.

Priority Claim

The Examiner indicates that the priority application does not provide support for the limitation of at least one nucleotide (dNTP) rendering TS-DNA resistant to nuclease activity following incorporated into the TS-DNA.

In response, Applicants first note that the Examiner's reference to priority Serial No. 09/605,592 is erroneous and should be 09/605,192 (see the filing receipt for the present application).

In addition, the parent application issued as a patent and the Applicants direct the Examiner's attention to claim 28 therein where this limitation is recited. Such claim was in the originally filed claim set of the priority case (as claim 28, dependent from claim 26, which depended from claim 1) and the entire disclosure of said application, which includes the claims, was incorporated by reference in the Preliminary Amendment filed simultaneously with the present application. Thus, claim 1 of the present application, as

well as all claims dependent on claim 1, are entitled to the filing date of the parent application (i.e., 28 June 2000).

Claim Objections

Claims 53 and 54 have been objected to on grounds that they recite the same subject matter. In response, Applicants have canceled claim 54.

Claim 61 was objected to as depending from claim 56 yet not reciting a limitation that is contained in the Markush Grouping of claim 56. In response, Applicant has canceled claim 61.

Rejection Under 35 U.S.C. 1.112

Claims 1, 5-9, 11-15, 20-25, 27, 29, 31-33, 35-39, 41, 42, 44-49, 51-59 and 61 were rejected under 35 U.S.C. 112, paragraph 1, as failing to meet the written description requirement.

These claims were rejected on grounds that an amendment submitted on 12 June 2002 included new matter, viz., a limitation of at least one nucleotide (dNTP) rendering TS-DNA resistant to nuclease activity following incorporation thereinto whereas the present application as filed, the original claims and the priority application all fail to recite this embodiment.

In response, Applicants direct the Examiner's attention to originally filed claim 28 of the parent application, priority application 09/605,192 (not 09/605,592, as stated in the rejection), now U.S. Patent No. 6,323,009 (as already discussed above regarding the priority claim). Said original claim 28 depends from claim 26 of the '592 patent, which

depends from original claim 1, so that said original claim 28 recites this embodiment. As already noted, the present application was filed along with a preliminary amendment that incorporated the priority claim and which has herein been amended to note that the parent application has issued as a patent. In the amendment of 12 June 2002, Applicants simply canceled claims 26 and 28 and wrote their limitations into claim 1. Applicants fail to see how this is new matter, especially since these same claims 26 and 28 were in the parent application as filed (now U.S. Patent 6,323,009) and were never canceled (thereby appearing in the issued patent and being present throughout prosecution, starting with the original priority application 09/605,192, filed 28 June 2000).

If these remarks do not succeed in resolving this matter then Applicants invite the Examiner to elaborate on the details of why claim 1 is believed to not be supported by the parent case (since its disclosure was incorporated by reference in its entirety when the present application was filed). Applicants further note that following the amendment of 12 June 2002 there was an intervening office action prior to the present one in which this ground of rejection does not appear to have been raised. If the Examiner believes that a simple change of language in claim 1 to reflect the desired limitations would be appropriate then Applicants' agent is fully prepared to discuss such an amendment.

Claim 35 was rejected under 35 U.S.C. 112, paragraph 2, as being indefinite for reciting "said at least one nucleotide" and depending from claim 1, which does not recite such nucleotide. In response, claim 35 has been amended to recite "said one such dNTP" which phrase is used in claim 1. Thus, this ground of rejection is believed moot.

In view of the foregoing claim amendments and remarks, Applicants believe that this ground of rejection has been overcome and respectfully request that the Examiner reconsider the claims.

Rejection Under 35 U.S.C. 103

Claims 1, 5-7, 11, 13, 15, 20-25, 27, 29, 31, 33, 35, 38, 39, 41, 44-49, 51-56 and 61 were rejected in ¶13 of the Office Action as unpatentable under 35 U.S.C. 103(a) over Lizardi (U.S. Pat. No. 5,854,033), Landers et al (U.S. Pat. No. 6,703,228) and Eckstein et al. (Trends in Bioch. Sci., Vol. 13(3), pp. 97-100 (1989)).

In response, Applicants note first that claims 54 and 61 have been canceled.

In rejecting claim 1, and the claims dependent therefrom, the Examiner relies on the Lizardi '033 patent as teaching a method of amplification comprising contacting multiple single-stranded non-circular random oligonucleotide primers (P1) with one or more amplification target circles (ATCs) wherein an ATC hybridizes to a plurality of said P1 primers.

In response, Applicants respectfully contend that the basic teaching of claim 1 is presented nowhere in the Lizardi '033 patent. Applicants note, initially, that while the Examiner points to specific citations for other elements of other claims, there is no specific citation to any column and line numbers of Lizardi suggesting use of multiple primers bound to the same ATC. In fact, there is no such teaching in Lizardi (and, indeed, there can be none). Because Lizardi et al is the main reference relied upon, yet does not provide a teaching of the fundamental limitations of claim 1, Applicants contend that it should not be relied on for an obviousness rejection. In addition, Applicants believe there are limitations recited in the Lizardi '033 patent that teach away from the claimed invention.

Claim 1 of the application recites, in pertinent part, "wherein an ATC hybridizes to a plurality of said P1 primers," meaning that the process generates an ATC that is hybridized to multiple P1 primers and whose amplification therefor produces

multiple tandem sequence DNA products. This is not taught by Lizardi or any of the other cited references, either alone or in combination.

Lizardi is directed to a method of rolling circle amplification, wherein an open circle probe (OCP), containing 5' and 3' segments (called "target probe portions") complementary to a single stranded target DNA sequence, is contacted with a target to which it hybridizes (see Figure 1 of Lizardi). This OCP is then ligated to form a circle (see Figure 2 of Lizardi). This is described in Lizardi as follows:

"An open circle probe (OCP) is a linear single-stranded DNA molecule...."
[Lizardi '033 at column 5, lines 22-23]

"The OCP has a 5' phosphate group and a 3' hydroxyl group. This allows the ends to be ligated using a DNA ligase, or extended in a gap-filling operation."
[Lizardi '033 at column 5, lines 26-28]

"Generally, an open circle probe is a single-stranded, linear DNA molecule comprising, from 5' end to 3' end, a 5' phosphate group, a right target probe portion, a spacer region, a left target probe portion, and a 3' hydroxyl group, with a primer complement portion present as part of the spacer region."
[Lizardi '033 at column 5, lines 41-46]

This OCP comprises a spacer region (separating the 5'- and 3'- probe portions) that contains a portion complementary to the primer sequence. When the primer is added, it binds to the primer complementary region and begins rolling circle amplification on the now ligated (i.e., closed) OCP (which is an ATC). Thus,

"The primer complement portion is part of the spacer region of an open circle probe. The primer complement portion is complementary to the rolling circle replication primer (RCRP). **Each OCP should have a single primer complement portion.** This

allows rolling circle replication to initiate at a single site on ligated OCPs." [emphasis added] [Lizardi '033 at column 6, lines 48-53]

Thus, each OCP should have a single primer complementary portion. If that is so then each OCP can bind only a single primer. Because the OCP is ligated to form an ATC, the ATC can have only a single primer complementary portion and therefor can bind only a single primer. As stated by Lizardi:

"Generally, an amplification target circle is a single-stranded, circular DNA molecule comprising a primer complement portion."

[Lizardi '033 at column 9, lines 37-39]

The ATC comprises a complementary portion, not multiple complementary portions. Further,

"Ligated open circle probes are a type of ATC, and as used herein the term amplification target circle includes ligated open circle probes. An ATC can be used in the same manner as described herein for OCPs that have been ligated."

[Lizardi '033 at column 9, lines 48-52]

An OCP that has been ligated has a single primer complementary portion and thus can bind only a single RCA primer.

"An amplification target circle, when replicated, gives rise to a long DNA molecule containing multiple repeats of sequences complementary to the amplification target circle. This long DNA molecule is referred to herein as tandem sequences DNA (TS-DNA)." [Lizardi '033 at column 9, lines 53-57]

Thus, the ATC, when replicated, gives rise to a TS-DNA (not multiple TS-DNAs that would be formed from multiple primers on the same ATC).

"A rolling circle replication primer (RCRP) is an oligonucleotide having sequence complementary to the primer complement portion of an OCP or ATC. This sequence is referred to as the complementary portion of the RCRP." [Lizardi '033 at column 10, lines 2-4]

Thus, the primer is complementary to "the" primer complement portion and not to "a" primer complement portion of the ATC. Figure 5 of Lizardi shows an open circle probe and there is only a single primer complementary portion.

"In general, the sequence of the RCRP can be chosen such that it is not significantly complementary to any other portion of the OCP or ATC." [Lizardi '033 at column 10, lines 8-11]

Thus, the primer is not complementary to any other portion of the ATC (such as additional complementary portions).

The teaching of Lizardi is presented in Figures 3, 8, 11a, 11b, 12, 13 and 14 therein. Not one of these figures depicts, or even suggests, multiple primers on a single ATC because nowhere in the Lizardi '033 is such a method disclosed. Figure 5 of Lizardi discloses that an OCP (such as an ATC) may have secondary target sequences but only a single primer complement. Additional target sequences are shown in Figure 12, where a secondary ATC is used to bind to these targets on the first ATC and then a secondary primer is used to amplify the second ATC. However, there is still no showing of multiple primers on a single ATC. Only Applicants disclose this and no specific teaching of this is identified in the Lizardi '033, apart from the Examiner's conclusory statement that Lizardi teaches such a method.

Applicants therefor believe that the requisite showing has not been made of the teaching of claim 1 regardless of what the additional references may disclose or how the references are combined because the element of multiple primers on a single ATC is

neither taught nor suggested by these references. Consequently, claim 1 is not rendered obvious by Lizardi in combination with any other references because none of these references teach the basic limitation of claim 1 that there be multiple primers on a single ATC.

In sum, Lizardi teaches only the amplification of an ATC using a single primer and not the multiple primers on a single ATC taught by Applicants.

The Examiner also refers to Lizardi at column 25, lines 36-49, as showing the use of secondary and tertiary primers in an SDCA process. However, this appears to be a reliance on language used in Lizardi without analysis of how it is used. Applicants direct the Examiner's attention to column 25, lines 24-35, which explains that the ATC is used as a template to form a first TS-DNA, to which secondary primers bind to generate a secondary TS-DNA to which tertiary primers bind (see Figure 11a and 11b of Lizardi). These tertiary primers are the secondary strand displacement primers and of course they are complementary to the ATC because the secondary TS-DNA is necessarily a tandem copy of the ATC sequence but Lizardi only teaches use of secondary and tertiary primers for amplification of TS-DNA and not for multiple TS-DNA products from the same ATC.

Further, because the ATC has only a single primer complementary portion, it can bind only a single primer at a time, irrespective of the presence of secondary and tertiary primers complementary to the ATC or OCP. The binding of multiple primers to the TS-DNA, either primary or secondary, is not encompassed by Applicants' claim 1 so that this embodiment of Lizardi does not fall within the limitations of claim 1 and therefor neither anticipates it nor renders it obvious.

Indeed, there is no reason to expect, based on Lizardi either alone or in combination with the other cited references, that multiple primers would operate with a single ATC. In the Lizardi method, the ATC contains probes complementary to a target DNA to which they hybridize followed by ligation. In the Lizardi method, shown in Figure 3,

the target DNA is still present and there is no teaching that multiple strand displacements can occur from multiple primers without involvement of the target (of which there is only one attached to the ATC). Applicants are the first to teach RCA using multiple primers on the same ATC with or without a target DNA being present.

As taught by Applicants, "In a specific embodiment, this aspect of the invention employs multiple primers (specific or random, exonuclease-sensitive or exonuclease-resistant) annealed to the circular target DNA molecules to increase the yield of amplified product from RCA. Multiple primers anneal to multiple locations on the circle and a product of extension by polymerase is initiated from each location. In this way multiple extensions are achieved simultaneously from a single amplification target circle." (see application at page 6, lines 2-9) This means that more than one primer must be simultaneously bound to the same ATC and none of the cited references, either alone or in combination, teach, or even suggest, such a method.

Claim 1 is directed to a method wherein an ATC becomes hybridized to a plurality of P1 primers (it is not just capable of doing this but does actually do this during the process, which is what this limitation means – see, for example, Figure 1 of the application). This means that during this process multiple primers become hybridized to the same ATC at the same time. None of the references suggest such a step, either alone or in combination with each other.

Consequently, there is no motivation to combine the random primers of Eckstein et al with Lizardi because Lizardi does not teach multiple P1 primers on the same ATC (since his method cannot use them – see above). Further, use of nucleotides to achieve TS-DNA resistance to nucleases if combined with Lizardi does not achieve the invention of claim 1 because Lizardi does not teach multiple P1 primers on the same ATC. Adding the random primers of Eckstein et al to these

two references does not make up for the fundamental deficiency of Lizardi in not teaching multiple P1 primers on a single ATC. Thus, no combination of these references achieves the invention of claim 1 even if they could be combined.

The rejection also notes a number of specific elements of claims dependent on claim 1 and which are urged to be in one or more of the recited references. However, Applicants note that because all of these claims depend from claim 1, either directly or indirectly, and since no combination of the claimed references renders claim 1 unpatentable, finding specific limitations in the different references fails to negate the patentability of claim 1, in which case claims dependent from claim 1 are likewise patentable.

In view of the foregoing, Applicants respectfully request that this ground of rejection be withdrawn.

Claims 12, 36 and 37 were rejected in ¶14 of the Office Action as unpatentable under 35 U.S.C. 103(a) over Lizardi (U.S. Pat. No. 5,854,033), Landers et al (U.S. Pat. No. 6,703,228) and Eckstein et al. (Trends in Bioch. Sci., Vol. 13(3), pp. 97-100 (1989)) and further in view of Rothberg et al (U.S. Pat. No. 6,274,320).

Here, the first 3 references are relied upon for rejection as already discussed while Rothberg et al is cited to show use of a solid support. In response, Applicants reiterate their above comments (without lengthy analysis) and urge that because claims 12 and 36 depend from claim 1, and claim 37 depends from claim 36, these claims are likewise patentable as is claim 1 irrespective of the Rothberg et al reference, which only adds the limitation of using a solid support. Because claim 1 is patentable over the 3 basic references, it must be patentable when an additional limitation is added.

In view of all of the previous remarks, Applicants respectfully request that this ground of rejection as it applies to claims 12, 36 and 37 be withdrawn.

Claims 14, 57 and 58 were rejected in ¶15 of the Office Action as unpatentable under 35 U.S.C. 103(a) over Lizardi (U.S. Pat. No. 5,854,033), Landers et al (U.S. Pat. No. 6,703,228) and Eckstein et al. (Trends in Bioch. Sci., Vol. 13(3), pp. 97-100 (1989)) and further in view of Navarro et al (J. Virol. Meth., Vol. 56, pp. 59-66 (1996).

Navarro et al is cited for use of RNA viroids. However, claims 14, 57 and 58 depend directly or indirectly from claim 1 and, because claim 1 is patentable over the 3 basic references, addition of Navarro et al adds little (and is irrelevant to claim 1 *per se*). Consequently, because claim 1 is patentable over the 3 basic references, it must be patentable when an additional limitation is added.

In view of all of the previous remarks, Applicants respectfully request that this ground of rejection as it applies to claims 14, 57 and 58 be withdrawn.

Claims 32, 42 and 59 were rejected in ¶16 of the Office Action as unpatentable under 35 U.S.C. 103(a) over Lizardi (U.S. Pat. No. 5,854,033), Landers et al (U.S. Pat. No. 6,703,228) and Eckstein et al. (Trends in Bioch. Sci., Vol. 13(3), pp. 97-100 (1989)) and further in view of Skerra et al (Nucleic Acids Research, Vol. 20, pp. 3551-3554 (1992).

Here, Skerra is cited for use of incorporation of a phosphorothioate nucleotide at the 3'-end of a primer to render it resistant to 3'-5' exonuclease activity of certain DNA polymerases. However, this limitation is not relevant to claim 1 and, because claim 1 is patentable over the 3 basic references, it must be patentable when an additional limitation is added.

In view of all of the previous remarks, Applicants respectfully request that this ground of rejection as it applies to claims 32, 34 and 59 be withdrawn.

Claims 1, 5-8, 11, 13, 15, 20, 21, 24, 27, 29, 31-33, 35, 38, 39, 41, 42, 44-49, 51-54 and 61 were rejected in ¶17 of the Office Action as unpatentable under 35 U.S.C. 103(a) over Dean et al. (Genome Res., Vol. 11, pp. 1095-1099 (2001) and Eckstein et al. (Trends in Bioch. Sci., Vol. 13(3), pp. 97-100 (1989)).

The Examiner contends that as to claim 1, Dean et al. teach amplification of vector DNAs, comprising contacting an ATC with random hexamer primers to form multiple tandem sequence DNA.

In response, Applicants urge that, regardless of what Dean et al discloses, Dean et al is not a valid reference against claim 1 because its publication date (given in the Office Action as 1 June 2001) is almost a year after the priority date of the present application (whose parent was filed 28 June 2000). Thus, Dean et al is not available as a reference regardless of what it teaches or what other reference, or references, it is combined with.

Applicants reiterate their above-recited arguments about the priority of this application. It is a divisional of Serial No. 09/605,192 (now U.S. patent 6,323,009) and contains identical disclosure. The Examiner has already attempted to argue that a prior amendment in this application attempted to add new matter. This is not true.

Based on the above remarks concerning new matter and the teaching of the claimed priority application, Dean et al is not available as a reference against the present application and Applicants have presented no further arguments about the merits of Dean's teaching (although Applicants note that the 3 inventors of the present application are the same individuals as 3 of the 4 authors of the Dean et al paper)

Claims 12, 22, 23, 36 and 37 were rejected in ¶18 of the Office Action as unpatentable under 35 U.S.C. 103(a) over Dean et al. (Genome Res., Vol. 11, pp. 1095-1099 (2001) and Eckstein et al. (Trends in Bioch. Sci., Vol. 13(3), pp. 97-100 (1989)) as applied to claim 1 and further in view of Rothberg et al (U.S. Patent No. 6,274,320).

In response, Applicants reiterate all of their above remarks regarding the Dean reference. Applicants reassert that this reference is not timely and claim 1 is patentable over it, however it is combined with Eckstein.

Rothberg et al is asserted as to other limitations found in the rejected claims, all of which depend either directly or indirectly, from claim 1.

Because Dean et al is not available as a reference against the present application, Applicants have presented no further arguments about the merits of Dean's teaching (although Applicants note that the 3 inventors of the present application are the same individuals as 3 of the 4 authors of the Dean et al paper)

Because claim 1 is patentable over the 2 basic references, it must be patentable when an additional limitation is added, regardless of how Rothberg et al is combined with the other references.

In view of all of the previous remarks, Applicants respectfully request that this ground of rejection as it applies to claims 12, 22, 23, 37 and 37 be withdrawn.

Claims 14, 25, 57, and 58 were rejected in ¶19 of the Office Action as unpatentable under 35 U.S.C. 103(a) over Dean et al. (Genome Res., Vol. 11, pp. 1095-1099 (2001) and Eckstein et al. (Trends in Bioch. Sci., Vol. 13(3), pp. 97-100 (1989)) as applied to claim 1 and further in view of Navarro et al (J. Virol. Meth., Vol. 56, pp. 59-66 (1996).

In response, Applicants reiterate all of their above remarks regarding the Dean reference. Applicants reassert that this reference is not timely and claim 1 is patentable over it regardless of how it is combined with Eckstein.

Navarro et al is asserted as to other limitations found in the rejected claims, all of which depend either directly or indirectly, from claim 1.

Because Dean et al is not available as a reference against the present application, Applicants have presented no further arguments about the merits of Dean's teaching (although Applicants note that the 3 inventors of the present application are the same individuals as 3 of the 4 authors of the Dean et al paper)

Because claim 1 is patentable over the 2 basic references, it must be patentable when an additional limitation is added, regardless of how Navarro et al is combined with the other references.

In view of all of the previous remarks, Applicants respectfully request that this ground of rejection as it applies to claims 14, 25, 57 and 58 be withdrawn.

Claims 55 and 56 were rejected in ¶19 of the Office Action as unpatentable under 35 U.S.C. 103(a) over Dean et al. (Genome Res., Vol. 11, pp. 1095-1099 (2001) and Eckstein et al. (Trends in Bioch. Sci., Vol. 13(3), pp. 97-100 (1989)) as applied to claim 1 and further in view of Sorge et al (U.S. Patent No. 5,556,722).

In response, Applicants reiterate all of their above remarks regarding the Dean reference. Applicants reassert that this reference is not timely and claim 1 is patentable over it, however it is combined with Eckstein.

Sorge et al is asserted as to other limitations found in the rejected claims, all of which depend either directly or indirectly, from claim 1.

Because Dean et al is not available as a reference against the present application, Applicants have presented no further arguments about the merits of Dean's teaching

(although Applicants note that the 3 inventors of the present application are the same individuals as 3 of the 4 authors of the Dean et al paper)

Because claim 1 is patentable over the 2 basic references, it must be patentable when an additional limitation is added, regardless of how Sorge et al is combined with the other references.

In view of all of the previous remarks, Applicants respectfully request that this ground of rejection as it applies to claims 55 and 56 be withdrawn.

The Commissioner is authorized to charge payment of any additional fees required with this communication or credit any overpayment to Deposit Account No. 03-0678.

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Alan J. Grant, Esq. **Date**

Respectfully submitted,

Alan J. Grant

Alan J. Grant, Esq.
Reg. No. 33,389

CARELLA, BYRNE BAIN, GILFILLAN,
CECCHI, STEWART & OLSTEIN
Six Becker Farm Road
Roseland, NJ 07068
Phone: 973-994-1700
Fax: 973-994-1744